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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,758	10/30/2001	Elma Tchilian	B0192/7034(KA/MXA)	8645

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Elizabeth R. Plumer
Wolf, Greenfield & Sacks, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, MA 02210-2211

EXAMINER
SAKELARIS, SALLY A

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 07/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/020,758	TCHILIAN ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *4 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-11, and 13-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Acknowledgement of claim to foreign priority of Application from The United Kingdom, 0114512.74 filed 6/14/2000 under 35 U.S.C. 119(a)-(d) has been made, and the certified copy of this foreign priority document has been received and as a result the claim to foreign priority under the same has been granted.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-3, 5-11, and 13-14 in the response dated 5/21/2003 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-3, 5-11, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of screening a human subject for susceptibility to developing HIV-1 infection, which method comprises screening for the presence or absence in the genome of the subject for the C77G mutation in the gene encoding CD45, does not reasonably provide enablement for a method of screening a human subject for susceptibility to all viral infections and immunodeficiency diseases and immunodeficiency diseases and/or pre-disposition to developing any severe disease following viral infection, which method comprises

screening for the presence or absence in the genome of the subject of one or more polymorphic variants or mutations in the gene encoding CD45 or of one or more polymorphic variants in linkage disequilibrium with or in close physical proximity to a polymorphic locus in the gene encoding CD45. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-3, 5-11, and 13-14 are broadly drawn to a method of screening a human subject for susceptibility to all viral infections and immunodeficiency diseases and/or pre-disposition to developing any severe disease following viral infection, which method comprises screening for the presence or absence in the genome of the subject of one or more polymorphic variants or mutations in the gene encoding CD45 or of one or more polymorphic variants in linkage disequilibrium with or in close physical proximity to a polymorphic locus in the gene encoding CD45. The specification teaches a method of screening a human subject for susceptibility to developing HIV-1 infection, wherein this method comprises screening for the presence or absence in the genome of the subject for the C77G mutation in the gene encoding CD45. The specification teaches the results of a study indicating that exon A (C77G) transversion and abnormal CD45 splicing are associated with HIV-1 infection. The specification teaches(Pg. 11) that out of 197 HIV-1 infected individuals, 11(5.6%) had the Exon A (C77) allele while out of

the 236 healthy donors only 4 (1.7%) had the same transversion. The specification then teaches that in one family, including "Patient W", who was diagnosed previously with haemophagocytic lymphohistiocytosis(HLH) also included his unaffected mom and two unaffected siblings all of whom were genotyped as having the same C77G mutation exhibiting phenotypically abnormal CD45 splicing. In addition, "Patient R" also diagnosed with HLH has an unaffected mother with the same C77G mutation exhibiting phenotypically abnormal CD45 splicing. The specification then teaches that in 21 other HLH patients, the mutant C77G allele was not found and that because "the number of subjects included in the study was very small...it is therefore impossible to draw statistically significant conclusions"(Pg. 15). The specification further teaches a single patient with CVID and a history of prolonged poliovirus excretion exhibited abnormal CD45 splicing caused by the C77G polymorphism(Pgs 15-17). The specification has not established a clear correlation between any viral infection other than HIV-1 and this C77G mutation. The specification teaches that the data presented with respect to HLH is not statistically significant because of the small sample size of only two families and 21 unrelated patients, it would be reasonable to expect that the data with respect to poliovirus is even less significant then, as the sample size is a single person. It is highly unpredictable then to anticipate how to apply these methods taught through the research on so few patients, not representative of large populations to a general population. The specification does not teach results from which one could extrapolate the present method of screening, applicable to any viral infection, or furthermore to any polymorphic variant other than the C77G mutation or those in linkage disequilibrium with or in close physical proximity to a polymorphic locus in the gene encoding CD45. More specifically, the specification does not teach the presence of an abnormal pattern of CD45

mRNA expression associated with the presence of a C77G mutant allele to be an indication of any susceptibility to any viral infection. The specification does not teach a method broadly drawn to screening a human subject for susceptibility to all viral infections and immunodeficiency diseases and/or pre-disposition to developing any severe disease following viral infection, which method comprises screening for the presence or absence in the genome of the subject of one or more polymorphic variants or mutations in the gene encoding CD45 or of one or more polymorphic variants in linkage disequilibrium with or in close physical proximity to a polymorphic locus in the gene encoding CD45.

As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate a method broadly drawn to screening a human subject for susceptibility to all viral infections and immunodeficiency diseases and/or pre-disposition to developing any severe disease following viral infection, which method comprises screening for the presence or absence in the genome of the subject of one or more polymorphic variants or

mutations in the gene encoding CD45 or of one or more polymorphic variants in linkage disequilibrium with or in close physical proximity to a polymorphic locus in the gene encoding CD45. One cannot anticipate any viral infection other than HIV-1, nor can they anticipate any mutation in CD45 other than C77G in exon A. Also, it is highly unpredictable to assume that one or more polymorphic variants or mutations in the gene encoding CD45 or of one or more polymorphic variants in linkage disequilibrium with or in close physical proximity to a polymorphic locus in the gene encoding CD45 will have the same effect as the C77G mutation. It is further unpredictable to assume that even this one mutation(C77G) will be associated to other viral infections absent any proof thereof. In the absence of specific guidance as to how to identify additional polymorphisms similarly related to C77G and to the susceptibility to developing a viral infection or an immunodeficiency disease, it would require undue experimentation to practice this method as it is so broadly claimed. The unpredictability is substantiated in the post filing date art through the teachings of Vorechovsky et al.(Nature 2001). The reference teaches a study to determine if the C77G mutation in CD45(aka PTPRC) modifies autoimmune disorders linked to the major histocompatibility locus. The results of the study show that there is no difference in the frequency of the C77G allele in patients and controls and therefore does not support a causative role for the polymorphism in the development of disorders with a strong autoimmune component etiology. This reference also teaches the same PCR based method of detection followed by digestion with *MspI* to identify the subjects' genotypes. Additionally, PTPRC(CD45) is taught to not be associated with the development of multiple sclerosis in US patients(Barcellos et al, Nature 2001), another immunodeficiency disease. This teaching further adds to the unpredictability involved when claiming a method of screening a

human subject for susceptibility to all viral infections and immunodeficiency diseases and/or pre-disposition to developing any severe disease following viral infection, which method comprises screening for the presence or absence in the genome of the subject of one or more polymorphic variants or mutations in the gene encoding CD45 or of one or more polymorphic variants in linkage disequilibrium with or in close physical proximity to a polymorphic locus in the gene encoding CD45. With respect to the present invention, one cannot readily anticipate the method's ability to screen for the susceptibility of a subject to developing a viral infection an immunodeficiency disease by detecting the presence or absence of a C77G mutation in the gene encoding CD45. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

The specification provides no guidance as to how to predictably identify additional samples wherein the claimed method includes a method of screening a human subject for susceptibility to all viral infections and immunodeficiency diseases and/or pre-disposition to developing any severe disease following viral infection, which method comprises screening for the presence or absence in the genome of the subject of one or more polymorphic variants or mutations in the gene encoding CD45 or of one or more polymorphic variants in linkage disequilibrium with or in close physical proximity to a polymorphic locus in the gene encoding CD45. will result in the detection of Pax 2 mRNA in a certain level in any sample other than tissue that would be correlated with prostate cancer. Furthermore, the specification fails to teach how these detected nucleic acids actually result in any of the claimed method's ability to predict susceptibility.

Consequently, the resulting screens for one or more polymorphisms will be variable and unpredictable, if not prophetic making the comparison of CD45 mutations and mRNA expression levels, not even defined in the specification, require undue experimentation. The ability to establish a correlation between the aforementioned methods and any mutation or level of mRNA detected from any nucleic acid in a method broadly drawn to determining the susceptibility of a human subject to all viral infections and immunodeficiency diseases and/or pre-disposition to developing any severe disease following viral infection, which method comprises screening for the presence or absence in the genome of the subject of one or more polymorphic variants or mutations in the gene encoding CD45 or of one or more polymorphic variants in linkage disequilibrium with or in close physical proximity to a polymorphic locus in the gene encoding CD45 can only be determined through extensive, random, trial and error experimentation. Therefore, neither the specification nor the art provides the guidance necessary to practice the method as claimed. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-11, and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1-3, 5-11, and 13-14 are indefinite over the recitation of "C77G" mutant. This phrase makes the claims unclear because the specification on page 11 in Table I, defines the mutant allele to be "C77" while the art refers to a 77 C to G transversion(Barcellos et al for example). It is not clear then whether the mutant allele is a "C" at position 77 or a "G". The claims should be amended to clarify in what nucleotide the mutation results.

B. Claims 1-3, 5-11, and 13-14 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are those that clarify how the detection of a C77G mutation or a CD45 mRNA expression pattern can be used to screen for susceptibility to viral infection and/or predisposition to developing severe disease following viral infection. It is therefore not clear whether the claims are intended to be limited to methods of detecting a mutant, polymorphic variant or methods of screening for susceptibility to viral infection. Appropriate clarification is needed.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 7:30AM-5:00PM and Friday from 1:00PM-5:00PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (703)308-2199. If attempts to reach the examiners are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)308-1119. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

7/8/2003

CARLA J. MYERS
PRIMARY EXAMINER